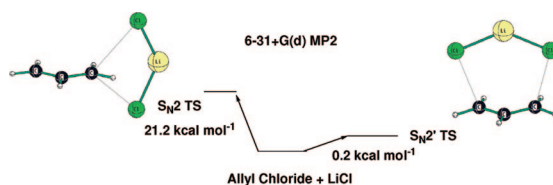# A Theoretical Study of S_N2' Reactions of Allylic Halides: Role of Ion Pairs

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Various disparate experimental results are explained by the hypothesis that reactions of anionic nucleophiles with allylic halides are generally S_N2. The S_N2' reactions that do occur proceed generally with *anti* stereochemistry. Reactions with ion pair nucleophiles occur preferentially as S_N2' reactions with *syn* stereochemistry. This hypothesis is consistent with a variety of computations at the HF, B3LYP, mPW1PW91 and MP2 levels with the 6-31+G(d) basis set of reactions of Li and Na fluoride and chloride with allyl halides and 4-halo-2-pentenes. Solvation is considered by a combination of coordination of dimethyl ether to the lithium and sodium cations and "dielectric solvation" with a polarized continuum model.

Introduction

The S_N2' reaction is a displacement reaction on allylic systems in which the entering nucleophile attacks an unsaturated carbon atom, C1, and the leaving group departs from the saturated C3.[1-6] This abnormal reaction involving concerted allylic rearrangement is considered to compete with the normal S_N2 reaction in which the entering and leaving groups are attached to the same carbon. The S_N2' reaction has a curious history that has been detailed by Magid in a thorough review that covers the literature through 1979.[7] There is also a more recent limited review by Paquette and Stirling.[8] The suggestion of *syn* stereochemistry to these reactions aroused much interest among organic chemists and led to many related experimental and theoretical reports. The first report came from an experimental investigation of the attack of piperidine and malonate on *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate in which the product was reported to have exclusively *syn* stereochemistry.[9,10]

A reexamination of this system demonstrated that the geometry can vary from predominantly *syn* to *anti* depending on the nature of the nucleophile.[11,12] It has been argued that the built-in conformational preferences of cyclohexenyl systems force *syn* attack.[13-15] Theoretical studies following thereafter showed preference for both *syn* and *anti* products, with the conclusion that S_N2' reactions do not possess any inherent stereochemical preference.[7,16-21] On the basis of primarily his studies on chloromethyl benzothiophene-1,1-dioxide, Bordwell questioned the concerted nature of the reaction.[1,22] Yates et al. suggested that the stereochemistry of these reactions depends on the electronic and steric nature of the substrate and the nucleophile.[23]

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Their studies predicted *syn* attack to be favored for neutral nucleophiles and *anti* attack for anions. In 1996, Borrmann and Stohrer reported more detailed higher level calculations of various anions with allyl chloride that showed a preference for *anti* reaction.[24] They suggested that Coulomb repulsion between incoming and leaving groups was the dominant factor. Lee et al. in their 1998 theoretical studies on the stereochemistry and concertedness of gas phase ionic identity S_N2' reactions also concluded that *anti* attack is preferred over *syn*.[25] More recently, Cramer et al. compared various nucleophilic substitution reactions among different allylic halides in various solvents.[26] They concluded that normal S_N2 reactions are preferred over the S_N2' reactions and that the difference is reduced with solvent polarity. They calculated *anti* attack to be favored over *syn* attack.

Over the years, the S_N2' reaction has evolved into a reaction of significance in synthetic organic chemistry. In particular, S_N2' reactions with organo-copper or mixed organo copper-zinc reagents lead to high regio- and stereoselectivity.[27] Advantage has been taken of this property to overcome some problems of stereocontrol in acyclic systems and in the synthesis of biologically active natural products. Copper N-heterocyclic carbene complexes catalyze highly S_N2'-selective allylic substitution reactions with Grignard reagents to give efficient enantioselective organic syntheses.[28] Additionally, Bailey et al. reported that the removal of a protecting allyl group from alcohols and phenols can be made easier by treatment with *t*-BuLi in hydrocarbons in reactions that involve S_N2' mechanisms.[29]

The S_N2' reaction is thus established as a significant and useful reaction in synthetic chemistry and well worth understanding. How then are we to reconcile the conflicting accounts of the several theoretical and stereochemical studies? We propose the following hypothesis: Reactions of allylic substrates with *anionic nucleophiles* are generally of the S_N2 type; when they do occur with S_N2' rearrangement the reaction occurs with *anti* stereochemistry. Allylic reactions with *ion pair nucleophiles* are generally of the S_N2' type and occur with *syn* stereochemistry. To our knowledge, this distinction between free ion and ion pair nucleophiles has never before been applied to the S_N2' reaction but the idea has been hinted at. For example, Bach[17] suggested that the stereochemistry results from "participation of the gegenion in the transition state" but without giving any further details. Borrmann and Storer[24] found *syn* stereochemistry by joining the allyl fluoride-fluoride ion TS with a $(Li-F-Li)^+$ bridge; this is equivalent to the S_N2' reaction of allyl fluoride with the lithium fluoride dimer, Li_2F_2, but this idea was never discussed as such.

The proposed role of ion pairs rationalizes many of the results. For example, many accounts of S_N2' regiochemistry involve reactions with high concentrations of nucleophile salts in relatively nonpolar solvents in which ion pairs are expected to predominate. Nevertheless, it is not possible to do more than rationalize the results because ion pairs were never considered in the past and their possible role was therefore never analyzed. In particular, most early studies were carried out in alcohols in which ion pairs and free ions can coexist and the product mixtures are impossible to disentangle. We can say, however, that by and large, the various experimental results are *consistent* with our hypothesis. Some experimental results are suggestive. Stork and Kreft[12] reported a reaction with sodium propanethiolate in boiling butanol (a relatively nonpolar solvent) that gave a mixture of S_N2 and S_N2' products in which the S_N2' products were 9:1 *syn*:*anti*. In hexamethylphosphoramide (a more polar solvent) the *syn*:*anti* S_N2' product ratio decreased to 60:40. We suggest that the ion pair reaction is more important in the less polar solvent. Nevertheless, we can only rationalize such experiments that were not carried out explicitly with ion pairs in mind. Ideally, the present proposal should be tested by using the Acree method,[30–32] or by examining reaction products and the stereochemistry of appropriate systems as a function of concentration or solvent polarity. Unfortunately, we are not in a position to carry out such experiments. Nevertheless, some studies in ether solvents are especially suggestive. Examples are the highly regiospecific S_N2' reactions of lithium salts in ether reported by Hagen et al.[33] and the evidence for exclusively S_N2' reactions with PhSK in glyme and with PhC≡CLi in THF provided by Stang and Dixit,[34] but these cases and others in ether solvents generally include other functional groups and are not simple or straightforward. Many examples, as reviewed by Paquette and Stirling[8] and by Woo and Keay[35] involve ring-opening or ring-closing reactions. The important feature of all of these cases is that the reactions are of the S_N2' type, with *syn* stereochemistry, and most probably involve ion pairs.

In this paper we examine our hypothesis computationally. Our aim is to determine the plausibility of S_N2' reactions of ion pairs particularly of contact ion pair lithium salts. We chose THF (as modeled by dimethyl ether, vide infra) as the solvent because free ions are usually less important in it. Ion pairs have long been considered to play a role in S_N2 reactions[30–32] and we have treated such reactions theoretically.[36–40] Although

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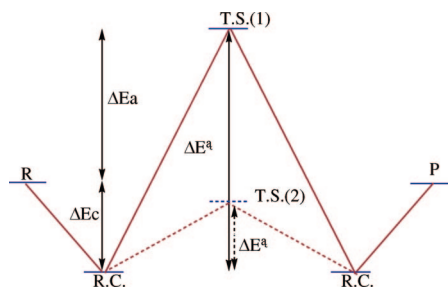(35) Woo, S.; Keay, B. A. *Synthesis* **1996**, 669–686.

FIGURE 1. Potential energy profile of identity S_N2 reactions. R, RC, TS, and P correspond to the energies of the separated reactants, the reaction complex (dipole−dipole complex for ion pair reactions and ion−dipole complex for ionic reactions), transition structure, and products. For identity reactions, R and P are equivalent. ΔE_c is the energy difference between reactants and reaction complex (complexation energy), ΔE_a is the energy difference between the separated reactants and the transition state, and $\Delta E^{\ddagger}$ is the energy difference between the reaction complex and the transition state. As shown by the dotted line, the transition state can in principle lie above (1) or below (2) the separated reactants (products).

many lithium salts are aggregated in THF,[41] the monomers frequently exist in sufficient concentration to be the actual reactants in some S_N2-type reactions.[42−45] In this paper we extend the computational studies to S_N2' reactions of monomeric ion pairs. Although we emphasize lithium salts, we have included some sodium salts for comparison. For computational simplicity, identity reactions have been considered where the leaving and the attacking nucleophiles are identical. The effect of ethereal solvents was modeled by coordinating the alkali cation with dimethyl ether; we have used this model previously for ion pair S_N2 reactions.[39] The computations were carried out for S_N2' reactions involving allyl, methylallyl and 1,3-dimethylallyl halides with the alkali metal halides in order to assess some substituent effects.

Computational Methodology[46]

The reactants chosen for the present study are allyl halides, $C_3H_3Y_2X$ (Y = H, CH_3; X = F, Cl) and metal halides, MX (M = Li, Na; X = F, Cl). The potential energy profile of a bimolecular nucleophilic substitution reaction in gas phase is generally described by a double well potential curve, which includes the reactants, an initial reaction dipole−dipole complex, the transition structure (TS), the product dipole−dipole complex and the separated products and is symmetrical in the case of identity reactions (Figure 1).

Optimizations of these points were done at the Hartree−Fock (HF) level using primarily the 6-31+G* basis set. Diffuse functions were used because of the importance of anions in these systems. A number of computations were also carried out at the MP2(Full) level for comparison. Additional calculations were added with two density functional methods. B3LYP is a popular hybrid method. The 6-31+G* basis set was used in all of these methods. Kormos and Cramer have studied the mPW1PW91 method in S_N2 reactions using the 6-31G(d) basis and found best results as a hybrid with incorporation of 58.1% of HF exchange.[26] We included a number of computations with this method and basis set (hereafter referred to as mPW1) for comparison. At each level the reactants and transition structures were optimized and the energy quantities reported are those for the geometry-optimized systems; e.g. 6-31+G* MP2(Full)//6-31+G* MP2(Full). All of the computations were done using various versions of the Gaussian program up to Gaussian03.[47] Vibrational frequency analyses were used to characterize the minima and transition states at each theory level used. The electron density distribution variations during the reaction were analyzed by calculating the natural charges using the NBO[48,49] method implemented in the Gaussian program. Thermodynamic functions were taken as calculated by Gaussian.[50] Note in particular that vibrations are treated as harmonic and that this assumption can lead to significant errors especially in the computation of entropies and free energies for the solvent-coordinated species which generally have several low vibrations. This point is discussed again below.

In previous computations[39] we have treated solvation of lithium compounds in ethers as a combination of chemical coordination of the ether to lithium and the *dielectric solvation* of the resulting supermolecule using a polarized continuum model (PCM).[51] This type of approach was also used by Yakimansky et al. in their modeling studies of anionic polymerization.[52] These authors used explicit coordination of THF with lithium in their computations, whereas we have generally used dimethyl ether as a computationally simpler model for THF. In the present work we use the IEF version of PCM[53] as implemented in Gaussian03. This approach and our use of the 6-31+G(d) basis set was tested by comparison with experimental data[54,55] for the dissociation of lithium chloride in THF. The results are summarized in Table 1. The use of bare lithium gives quite poor results. Lithium cation in THF is known to be coordinated to four solvent molecules[56] and is clearly not adequately modeled by dielectric solvation alone. On the other hand, treatment of the specifically coordinated cation, even with dimethyl ether as a model for THF, gives results in quite good accord with experiment for three of the methods. The mPW1 method fails this test. The dielectric solvation is only slightly dependent on basis set. Also noteworthy is that HF gives results comparable to MP2 and better than B3LYP. There may well be some fortuitous cancelation of errors but these results do suggest that this approach and theory level, except for mPW1, are adequate for the present purpose.

A number of energies are presented as the electronic energies with correction for computed zero point energies (ZPE). Some

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**TABLE 1. Dissociation of LiCl in THF; Energies Given as kcal mol⁻¹, E = Me$_2$O**

	HF	MP2	B3LYP	mPW1	expt
		reaction: LiCl = Li⁺ + Cl⁻			
$\Delta(E_0 + ZPE)$	147.33	152.21	150.06	163.53	
$\Delta(G + E_{Thermal})$	160.34	165.22	163.06	176.54	
ΔG_{solv}	−134.58	−134.91	−135.09	−138.76	
$\Delta(G + G_{solv})$	25.76	30.31	27.97	37.78	13.5[a], 14.2[b]
		reaction: LiCl·3E + E = Li⁺·4E + Cl⁻			
$\Delta(E_0 + ZPE)$	85.45	88.36	89.95	79.86	
$\Delta(G + E_{Thermal})$	99.84	100.97	102.19	89.56	
ΔG_{solv}	−82.22	−83.58	−83.10	−87.30	
$\Delta(G + G_{solv})$	17.62	17.39	19.09	2.26	15.0, 15.7[c]

[a] Reference 54. [b] Reference 55. [c] The equilibrium constants were divided by [THF] = 12.3 M to put them in the same units as the computed equations.

previous results cited will also differ slightly (about 0.1 kcal mol⁻¹) from those published because the ZPE correction factor of 0.9153 was not applied here. This correction factor was also not applied in the use of the frequencies by Gaussian to compute the thermodynamic constants, notable the free energy, also presented. In several cases another structure was found for the reaction complex lower in energy than that reported previously. Bond lengths, natural charges, and reaction energies and barriers are tabulated in Tables S1−S7 (Supporting Information). Energies and Cartesian coordinates of all of the structures at the various levels computed for this paper are given in Table S8 (Supporting Information).

Results and Discussion

The general results are highlighted by those of the prototypical reactions of allyl chloride with lithium chloride and chloride ion summarized in Table 2. The results are presented according to eqs 1 and 2 in which a common reaction complex (RC) is assumed to precede the isomeric reactions. Equations 1−3 also define the energy quantities ΔE_c, $\Delta E^{\ddagger}$, and ΔE_a. ΔE_c corresponds to an equilibrium between the RC and the reactants. All of the atoms involved in the reaction are thus in the RC and the reaction itself is then an isomerization of the RC. Isomeric reactions can be compared by $\Delta\Delta E_a$ or by $\Delta\Delta E^{\ddagger}$.
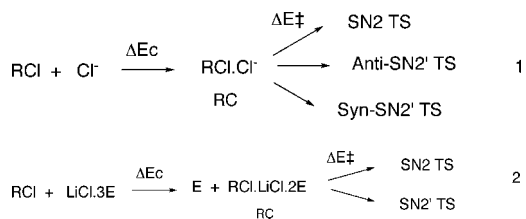
$$\Delta E_a = \Delta E_c + \Delta E^{\ddagger} \qquad (3)$$

The HF structures and transition structures are depicted in Figures 2 and 3. The structures are generally similar at the other theory levels except that the partial bonds to chlorine are generally somewhat shorter. These structures are shown in Figures S1−S6 (Supporting Information). The principal difference is the S$_N$2 transition structure with LiCl·2E at MP2. This structure does not have equivalent chlorines and corresponds to the S$_N$2 type II transition structures discussed in a previous paper.[39] Note that in eq 2, the ether in one coordination site of LiCl·3E is replaced by allyl chloride to form the RC and the lithium cation stays four-coordinate throughout the reaction.

The individual energy magnitudes depend on the method used but all show the same general trends. In particular, the general results are the same for the gas phase or with addition of dielectric solvation; the ΔE (E + ZPE) and ΔG (G + $E_{thermal}$) results give the same order of reactivities. For the ionic nucleophile, chloride ion, the S$_N$2 reaction has the lowest barrier and the S$_N$2′ reaction with *anti* incoming and leaving groups is more facile than the *syn* reaction in which the chlorides are on the same side. Park et al.[25] have also reported on the S$_N$2 and S$_N$2′ reactions of allyl chloride with chloride ion with somewhat larger basis sets and included higher theory levels. Their results and conclusions are essentially the same as ours.[57] The same order of reaction barriers, S$_N$2 < S$_N$2′ *anti* < S$_N$2′ *syn*, was also found by Kormos and Cramer[26] with their modified mPW1 method; in addition they showed this reactivity order to persist in solutions modeled with a dielectric continuum. Similarly, Borrmann and Stohrer[24] found the *anti* TS more stable than *syn* and invoked electronic reasons.

For the ion pair nucleophile, LiCl coordinated with dimethyl ether, the results are totally different. The *syn* S$_N$2′ reaction now has the lowest barrier and is preferred to S$_N$2. This result is readily rationalized by the electrostatic stabilization of the two *syn* chlorides by the metal cation in the six-membered ring transition structure as shown in Figure 3. The reaction barriers for the LiCl ion pair reactions are generally higher than for reactions of free chloride ion, but these barriers correspond approximately to rate constants rather than rates. In ethers ionic dissociation is so low that the concentrations of chloride ion are low and reaction *rates* with chloride ion would also then be low. The concentration of chloride ion could be made even lower by addition of lithium salts of non-nucleophilic anions.

These results are consistent with our hypothesis. To establish generality we extended the computations to LiF, NaF and NaCl reacting with the corresponding allyl halides and 3-halo-2-pentenes (Table 3). The 3-halo-2-pentenes (1,3-dimethylallyl halides) were chosen so that S$_N$2′ reactions would be identity reactions, avoiding the crotyl-α-methylallyl isomerization problem. Fluorides were included to provide further generalizations although allyl fluorides sometimes behave anomalously in S$_N$2-type computations.[40,58] In the present case they mostly behave normally but sometimes show different trends from the chlorides. For example, most of the MP2 barriers for the S$_N$2′ reactions of chloride ion pairs differ from the HF barriers by only a few kcal mol⁻¹ but the differences are greater for the fluorides. Accordingly, in this discussion, we will emphasize the reactions of the chlorides.

Sodium cation, being bigger than lithium can involve higher coordination numbers and weaker coordination bonds. In order to model these effects we computed the reactions of the lithium and sodium halides with varying degrees of coordinated solvent, MX.nE, from $n = 0$ to n = 2; that is, the general ion pair reactions are of the form in equation 4.

$$RX + MX{\cdot}nE = RX{\cdot}MX{\cdot}nE(RC) = TS \qquad (4)$$

For simplicity and in order to evaluate generalizations, only the $\Delta(E + ZPE)$ values are recorded without dielectric solvation (e.g., in the gas phase). It was shown above that the general results do not depend on entropy changes, the thermal energies or dielectric solvation. All of the results pertain to *syn* ion pair

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(58) Lee, I.; Kim, C. K.; Chung, D. S.; Lee, B.-S. *J. Org. Chem.* **1994**, *59*, 4490–4494.

TABLE 2. Energy Quantities for Reactions of Allyl Chloride with LiCl or Chloride Ion with Various Theory Levels at 6-31+G* (mPW1 at 6-31*) in kcal mol^{-1a}

	ΔE_c				$\Delta E^{\ddagger}$				ΔE_a			
	HF	MP2	B3LYP	mPW	HF	MP2	B3LYP	mPW	HF	MP2	B3LYP	mPW
				nucleophile and reaction: LiCl·3E, S_N2'								
$\Delta(E_0 + ZPE)$	3.03		2.40	−3.89	21.61		11.95	21.07	24.64	26.33	14.35	17.18
$\Delta(G + E_{Thermal})$	1.50		0.96	−5.29	24.49		14.37	23.96	25.99	29.87	15.34	18.68
ΔG_{solv}	5.43		4.94	4.74	−2.82		2.07	3.39	2.61	6.86	7.01	8.13
$\Delta(G + G_{solv})$	6.93		5.90	−0.55	21.67		16.44	27.36	28.60	36.73	22.35	26.81
				nucleophile and reaction: LiCl·3E, S_N2								
$\Delta(E_0 + ZPE)$	3.03		2.40	−3.89	31.11		27.00	38.23	34.14	44.73	29.39	34.33
$\Delta(G + E_{Thermal})$	1.50		0.96	−5.29	32.90		28.85	40.04	34.40	46.97	29.81	34.76
ΔG_{solv}	5.43		4.94	4.74	−9.99		−3.66	−4.25	−4.56	−1.56	1.28	0.49
$\Delta(G + G_{solv})$	6.93		5.90	−0.55	22.91		25.19	35.79	29.84	45.41	31.09	35.25
				nucleophile and reaction: Cl^-, S_N2								
$\Delta(E_0 + ZPE)$	−9.11	−11.96	−10.52	−15.38	17.69	19.10	9.59	10.96	8.58	7.14	−0.92	−4.42
$\Delta(G + E_{Thermal})$	−12.67	−15.09	−13.80	−18.50	18.43	19.61	10.18	11.43	5.76	4.51	−3.63	−7.07
ΔG_{solv}	11.11	11.90	11.77	14.14	0.02	1.75	3.79	4.34	11.13	13.65	15.56	18.48
$\Delta(G + G_{solv})$	−1.56	−3.19	−2.03	−4.36	18.45	21.36	13.97	15.77	16.89	18.16	11.93	11.41
				nucleophile and reaction: Cl^-, S_N2' *anti*								
$\Delta(E_0 + ZPE)$	−9.11	−11.96	−10.52	−15.38	24.16	23.88	11.67	12.93	15.04	11.93	1.15	−2.44
$\Delta(G + E_{Thermal})$	−12.67	−15.09	−13.80	−18.50	25.15	25.00	12.73	13.96	12.49	9.90	−1.07	−4.54
ΔG_{solv}	11.11	11.90	11.77	14.14	−3.23	4.35	5.27	6.48	7.88	16.25	17.04	20.62
$\Delta(G + G_{solv})$	−1.56	−3.19	−2.03	−4.36	21.92	29.35	18.00	20.44	20.37	26.15	15.97	16.08
				nucleophile and reaction: Cl^-, S_N2' *syn*								
$\Delta(E_0 + ZPE)$	−9.11	−11.96	−10.52	−15.38	31.46	26.44	15.77	16.84	22.34	14.48	5.25	1.47
$\Delta(G + E_{Thermal})$	−12.67	−15.09	−13.80	−18.50	32.20	27.29	16.50	17.55	19.53	12.20	2.70	−0.95
ΔG_{solv}	11.11	11.90	11.77	14.14	−6.65	2.18	2.32	3.73	4.46	14.08	14.09	17.87
$\Delta(G + G_{solv})$	−1.56	−3.19	−2.03	−4.36	25.55	29.47	18.82	21.28	23.99	26.28	16.79	16.92

^{a} ΔE_c is the energy of formation of the reaction complex from the separated reactants; ΔE_a is the barrier height relative to the separated reactants; $\Delta E^{\ddagger}$ is the TS energy relative to the reaction complex. E is the coordinated solvent, dimethyl ether.
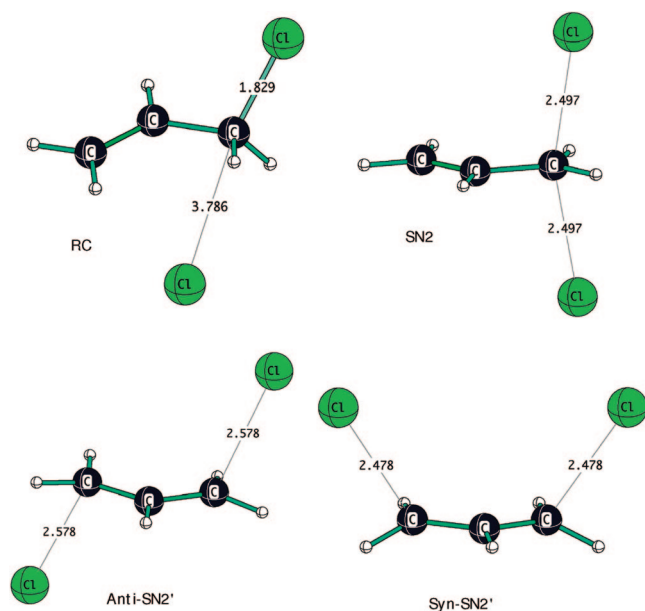
FIGURE 2. Optimized geometries of reaction complex and transition structures obtained at RHF/6-31+G* for reactions of allyl chloride with Cl^-.

S_N2' transition structures. The corresponding *anti* ion pair TSs are, as expected, much higher in energy; for LiCl the *anti* S_N2' TS is 44.5 kcal mol^{-1} higher than *syn* (HF) while for coordination with one dimethyl ether, the difference is 35.8 kcal mol^{-1}. These numbers are so high that such *anti* ion pair S_N2' reactions are not considered further; however, their TS structures are shown in Figure 4.

As in Table 2, the B3LYP results in Table 3 often differ strikingly from the other results. Remarkably, however, the mPW1 barriers in Table 3 are quite similar to MP2 and generally
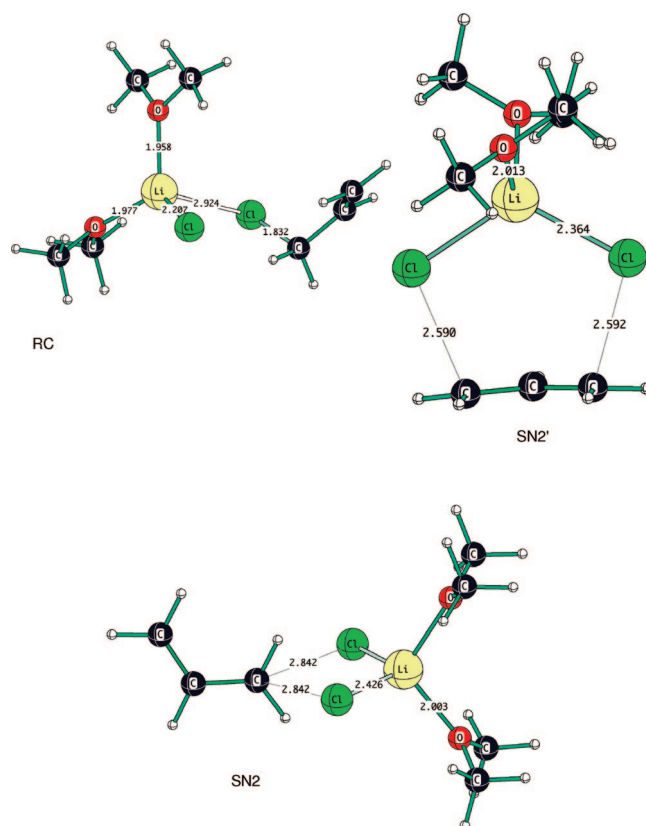
FIGURE 3. Optimized geometries of reaction complex and transition structures obtained at RHF/6-31+G* for reactions of allyl chloride with LiCl·2E (E = dimethyl ether).

differ by only a few kcal mol^{-1}. This method could thus prove to be quite useful since it is computationally much less intensive.
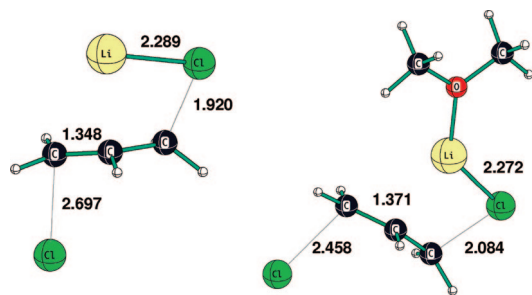
FIGURE 4. Optimized geometries for *anti* ion pair S_N2' transition structures at RHF/6-31+G* for reactions of allyl chloride with LiCl and LiCl·E.
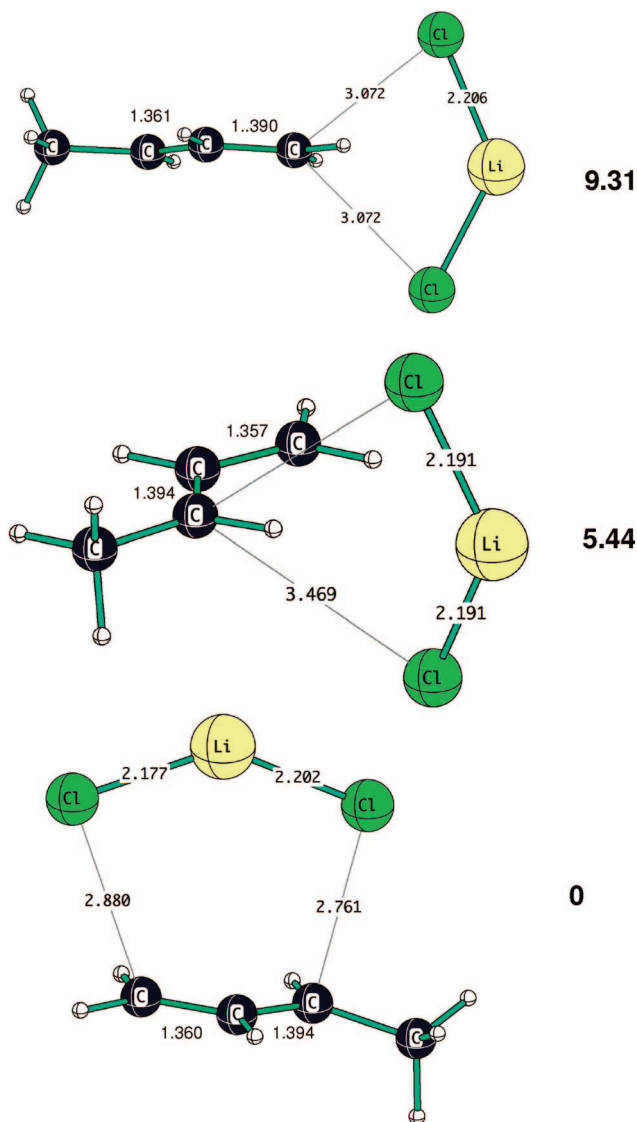

FIGURE 5. Isomeric transition structures for S_N2 and S_N2' reactions of crotyl chloride and α-methylallyl chloride with LiCl. Numbers given are the relative energies in kcal mol^{-1} for HF 6-31+G(d) given as $\Delta(E_0 + ZPE)$. The upper structure is crotyl chloride−LiCl S_N2, the middle structure is α-methylallyl chloride−LiCl S_N2 and the bottom structure, the most stable, is the S_N2' TS.

With the possible exception of the lithium halides with two coordinated solvents, these alkali halides are not realistic models for ethereal solutions. Nevertheless, several useful generalizations can be made. At all theory levels, as ether is coordinated to the metal cation the reaction barriers increase. Coordination

of the metal to the leaving halide is important and successive coordinations are increasingly less exothermic. These increases in ΔE a are smaller for successive coordination with sodium than for lithium and can be rationalized by the greater size of sodium.

Coordination of alkali halide with allyl halide to form the RC also becomes less exothermic as ethers are coordinated to the metal. The dipole−dipole reaction complexes involve only small changes in the structures of the reactants; for example, the C−Cl bond distance in allyl chloride at HF/6-31+d level is 1.804 Å and increases to 1.857 Å in the allyl chloride−LiCl RC. The Li−Cl bond length in LiCl·nE is longer as dimethyl ethers are coordinated to the lithium, an expected consequence of charge-dipole repulsion between chloride ion and ether. The Li−Cl bond length increases from 2.067 to 2.093 and 2.152 Å as one and two dimethyl ethers coordinate. These values increase by about another 0.05 Å with further coordination to allyl chloride to form the RC.

This principle holds as well for the transition structures. With additional coordination of lithium with ether, the bond to Cl increases, and, concomitantly, the bond distance between Cl and the terminal allylic carbons decreases. The corresponding reaction barriers also increase. In all of the theory methods LiCl has lower barriers than NaCl but the two become comparable or of inverted order by the time two ethers have coordinated to the metal.

Note further that in S_N2 reactions of allyl halides, the allyl single and double bonds change only slightly in the TS compared to reactant.[40] In S_N2' reactions, however, these bonds become equivalent (1.376 Å) and, indeed, are quite close to the C−C bond distance in allyl cation, 1.374 Å (both at HF/6-31+G*). This correspondence suggests that the ion pair S_N2' transition structures might themselves be regarded as oriented tight ion pairs between allyl cation and the metal dihalide anions. We will return to this point later.

Finally, the ΔE_a barriers are lower at all levels for the dimethylallyl systems. This result is opposite that of most S_N2 reactions in which α-substitution generally decreases reactivity. For a further test of substituent effects we did a limited study of the crotyl−α-methylallyl system augmenting some calculations published previously.[40] Three transition structures are isomeric and are shown in Figure 5. The most stable structure is S_N2' and the least stable is the S_N2 TS of crotyl chloride and LiCl. In all cases the double and single bonds of the allylic reactants have become almost equal in length and similar to that of the allyl cation. That is, all three TSs resemble ion pairs of crotyl cation and LiCl$_2^-$ except that they all have the single negative frequencies characteristic of TSs.

The suggestion that these S_N2' transition structures resemble ion pairs of allylic cation finds additional support in the reduced natural charges (charges with hydrogens incorporated into the attached atoms) illustrated in Table 4 for the S_N2' reaction of allyl chloride with LiCl. The reaction complex shows relatively small changes from the separated reactants; the changes are those expected from mutual polarization. The changes are much greater for the transition structure; in particular, the allyl moiety resembles that of allyl cation. The reduced natural charges for the 1,3-dimethylallyl chloride−LiCl system in Table 5 quantify this point. The total charge of the allyl moiety in the S_N2' allyl TS is 0.753. The corresponding charge of the dimethylallyl moiety is 0.949, showing that this TS is very much an allylic cation−LiCl$_2^-$ ion pair. The HF and MP2 methods give

TABLE 3. Ion Pair S$_N$2′ Reactions of Uncoordinated and Me$_2$O-Coordinated Alkali Halides with Allyl and α,γ-Dimethylallyl Halides^a

| | C$_3$H$_5$X reactions | | | | | | | | |
| | ΔE$_a$ | | | ΔE‡ | | | ΔE$_c$ | | |
MX	HF	DFT	MP2	HF	DFT	MP2	HF	DFT	MP2
LiF	7.77	−6.09	−3.52	24.07	11.00	16.93	−16.30	−17.08	−20.45
		−5.08			16.48			−21.56	
LiF·E	13.84	−0.91	−0.42	26.84	13.08	18.44	−13.00	−13.99	−18.86
		−1.06			17.93			−18.99	
LiF·2E	20.82	5.94	b	29.39	15.23	b	−8.58	−9.29	b
	(29.19)	5.70			20.82			−15.12	
LiCl	1.31	−7.14	0.18	14.48	7.19	17.66	−13.17	−14.33	−17.48
		0.77			16.09			−15.32	
LiCl·E	8.92	−0.81	4.77	18.00	9.54	20.21	−9.08	−10.35	−15.45
		6.30			18.41			−12.11	
LiCl·2E	16.20	5.70	8.34	21.61	11.95	b	−5.40	−6.24	b
	(24.64)	12.76			21.07			−8.31	
NaF	8.65	−5.72	−3.23	23.28	9.70	15.03	−14.63	−15.42	−18.26
								−22.43	
NaF·E	11.17	−2.45	−0.90	24.46	11.59	16.69	−13.29	−14.05	−17.59
		−5.09			15.37			−20.46	
NaF·2E	14.34	1.03	b	26.18	13.68	b	−11.84	−12.65	b
	(22.29)	−1.68			16.80			−18.48	
NaCl	4.81	−3.89	4.13	16.16	8.19	19.37	−11.35	−12.07	−15.24
		3.53			17.33			−13.81	
NaCl·E	7.84	−1.41	5.52	18.02	9.61	21.14	−10.18	−11.03	−15.62
		6.38			18.86			−12.47	
NaCl·2E	11.60	1.74	b	20.33	11.29	b	−8.73	−9.55	b
	(21.63)	9.80			20.55			−10.75	

| | 1,3-(Me)$_2$C$_3$H$_3$X reactions | | | | | | | | |
| | ΔE$_a$ | | | ΔE‡ | | | ΔE$_c$ | | |
MX	HF	B3LYP	MP2	HF	B3LYP	MP2	HF	B3LYP	MP2
LiF	0.50	−9.56	−7.63	18.56	10.09	15.97	−18.07	−19.65	−23.60
		−6.46			16.43			−22.89	
LiF·E	8.62	−3.02	−3.10	22.78	12.37	17.59	−14.16	−15.39	−20.69
								−20.12	
LiF·2E	17.38	4.88	b	26.57		b	−9.19	−15.97	b
	(25.76)	5.72			21.69				
LiCl	−10.52	−11.42	−4.87	4.53	5.10	14.96	−15.06	−16.52	−19.83
		−4.29			12.57			−16.86	
LiCl·E	−1.06	−4.11	b	9.24	7.72	b	−10.30	−11.83	−17.75
		2.41			15.59			−13.88	
LiCl·2E	7.79	3.45	b		14.04	b		−6.25	b
	(16.22)	9.74			19.21			−9.47	
NaF	6.11	−6.33	−4.59	21.47	10.17	14.81	−15.36	−16.50	−19.39
		−10.97			10.89			−21.86	
NaF·E	10.09	−2.40	−1.87	23.26	11.69	16.55	−13.16	−14.10	−18.42
		−5.88			13.35			−19.23	
NaF·2E	14.19		b	25.28		b	−11.09		b
	(22.14)	−0.94			16.15			−17.10	
NaCl	−5.84	−6.63	0.40	7.14	7.28	18.27	−12.97	−13.91	−17.87
		0.18			15.83			−15.64	
NaCl·E	−1.76	−3.46	b	8.90	8.01	b	−10.66	−11.47	b
		3.73			16.95			−13.23	
NaCl·2E	2.89	0.40	b	12.36	10.82	b	−9.47	−10.42	b
	(12.92)	7.93			19.29			−11.37	

^{a} ΔE$_a$ = E(TS) − E(reactants), ΔE‡ = E(TS) − E(RC), and ΔE$_c$ = E(RC) − E(reactants) in kcal mol^{-1} at HF, DFT, and MP2 levels for the reactions: RX + MX·nE = RX·MX·nE(RC) = TS. The DFT values are given as B3LYP (top) and mPW1 (bottom, italics). The energy of the equation MX·3E + RX → TS·2E + E is also given in parenthesis for HF ΔE$_a$. E is the coordinated solvent, dimethyl ether. X = F, Cl; M = Li, Na. ^{b} Only optimizations were done; frequencies were not obtained.

TABLE 4. Reduced Natural Charges (HF/6-31+d) Calculated for the Reaction of Allyl Chloride (shown as CH$_2$=CH−CH$_2$−Cl) and LiCl

	CH$_2$	CH	CH$_2$	Cl	Li	Cl
separated reactants	0.034	−0.004	0.078	−0.107	0.941	−0.941
reaction complex	0.166	−0.058	0.117	−0.196	0.900	−0.930
transition structure	0.490	−0.227	0.490	−0.826	0.899	−0.826

comparable results for the natural charges, while the B3LYP method gives values that are substantially lower.

Further trends are shown in the reduced natural charges of the other identity S$_N$2′ reactions of allyl halides in Table 6. As LiCl is coordinated with dimethyl ethers, its effective electropositivity decreases and the total charge of the allyl moiety changes from 0.753 to 0.723 to 0.689 with coordination of 0, 1 and 2 ethers, respectively. Unexpectedly, NaCl is effectively less electropositive than lithium by this measure but also changes less with coordination with ether; the total allyl charge changes from 0.733 to 0.713 to 0.697 by coordination of sodium with 0, 1 and 2 ethers, respectively. These trends are reproduced by

TABLE 5. Reduced Natural Charges Calculated for the Reaction Complex (RC) and Transition Structures (TS) in the Gas-Phase S_N2' Reactions of 1,3-(Me)$_2$C$_3$H$_3$X + MX from NBO Analysis (RHF/ 6-31+G*)

				reaction complexes, RC			
M	X	C1	C2	C3	X1	M	X2
Li	F	0.444	−0.147	0.151	−0.520	0.961	−0.972
Li	Cl	0.127	−0.079	0.121	−0.237	0.898	−0.929
Na	F	0.438	−0.163	0.160	−0.512	0.981	−0.984
Na	Cl	0.085	−0.101	0.112	−0.194	0.935	−0.956

|			transition structures, TS		
M	X	C1	C2	X	M
Li	F	0.491	−0.272	−0.899	0.965
Li	Cl	0.513	−0.228	−0.922	0.895
Na	F	0.466	−0.309	−0.854	0.983
Na	Cl	0.518	−0.233	−0.950	0.946

TABLE 6. Reduced Natural Charges Calculated for the Reaction Complex (RC) and Transition Structures (TS) of S_N2' Reactions of C$_3$H$_5$X + MX·nE (n = 1, 2) from NBO analysis (RHF/6-31+G*)[a]

	reaction complexes, RC·nE					
	C1	C2	C3	X1	M	X2
LiF	0.490	−0.103	0.133	−0.513	0.965	−0.972
LiF·E	0.489	−0.095	0.115	−0.496	0.927	−0.963
LiF·2E	0.483	−0.075	0.082	−0.480	0.900	−0.956
LiCl	0.166	−0.058	0.117	−0.196	0.900	−0.930
LiCl·E	0.158	−0.050	0.100	−0.183	0.875	−0.924
LiCl·2E	0.135	−0.035	0.074	−0.163	0.877	−0.929
NaF	0.489	−0.105	0.122	−0.508	0.982	−0.981
NaF·E	0.486	−0.099	0.114	−0.502	0.973	−0.977
NaF·2E	0.483	−0.083	0.094	−0.491	0.960	−0.974
NaCl	0.160	−0.055	0.108	−0.201	0.943	−0.955
NaCl·E	0.154	−0.052	0.101	−0.190	0.931	−0.954
NaCl·2E	0.140	−0.042	0.084	−0.169	0.921	−0.952

	transition structures, TS·nE				
	C1	C2		X	M
LiF	0.505	−0.324		−0.825	0.962
LiF·E	0.480	−0.361		−0.773	0.924
LiF·2E	0.459	−0.403		−0.731	0.897
LiCl	0.490	−0.227		−0.826	0.899
LiCl·E	0.475	−0.227		−0.811	0.876
LiCl·2E	0.459	−0.229		−0.798	0.868
NaF	0.440	−0.481		−0.682	0.965
NaF·E	0.432	−0.490	0.431	−0.663	0.948	−0.668
NaF·2E	0.425	−0.488		−0.660	0.938
NaCl	0.482	−0.231		−0.841	0.947
NaCl·E	0.472	−0.231		−0.830	0.933
NaCl·2E	0.464	−0.231		−0.821	0.921

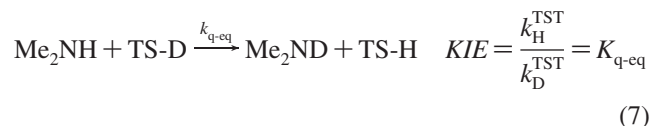[a] E is the solvent, dimethyl ether.

the MP2 and B3LYP methods as well. Coordination of the metal cation with dimethyl ether generally increases the barrier. This effect can be understood in terms of the ether binding more strongly to the reactant metal halide than to the additionally coordinated metal cation in the TS.

One other point needs to be discussed. The S_N2' reaction of allylic halides with amines has long been known. The faster reaction of secondary compared to tertiary amines was interpreted at least as long ago as 1951[6] in terms of a cyclic transition structure with hydrogen bonding from the entering nitrogen to the leaving halide. This type of TS has a clear analogy to the ion pair structures discussed above with a proton taking the place of the alkali cation. In 1964, Dittmer and Marcantonio showed that the second order reaction of 3-chloro-1-butene with *N*-methylaniline-*N-d* shows at best only a small kinetic isotope
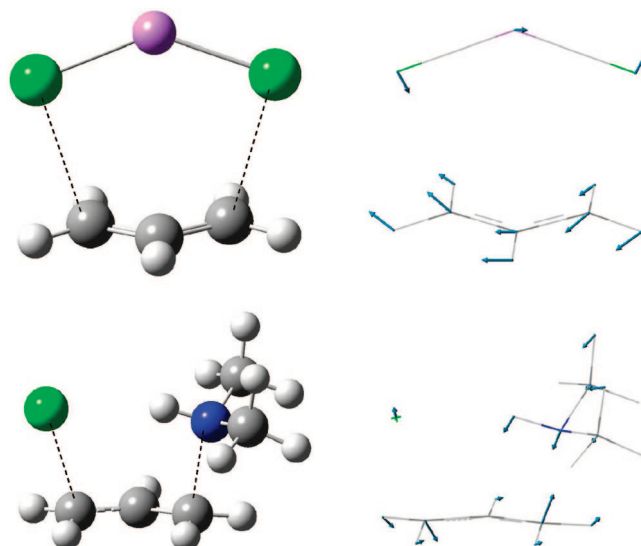
FIGURE 6. S_N2' TS for allyl chloride−LiCl is shown above with the displacement vectors for the imaginary frequency on the right. The TS for the reaction of allyl chloride with dimethylamine is shown below with the displacement vectors for the imaginary frequency on the right. Bond distances are C−Cl, 2.381 Å; N−(allyl)C, 2.102 Å; N−H, 1.007 Å; Cl−H, 2.415 Å (HF6-31+G(d,p)).

effect (KIE).[59] This result raises questions about the presumed role of hydrogen bonding and the nature of the S_N2' transition states. Accordingly, we examined the model reaction of dimethylamine with allyl chloride and computed the isotope effect for Me$_2$ND at HF 6-31+G(d,p). The computed transition structure shown in Figure 6 is as expected but with a long Cl−H bond of 2.415 Å, a rather long and weak hydrogen bond.

We have previously discussed computations of isotope effects in ionic and ion-pair reactions.[60] Briefly, within the quasi-thermodynamic formulation of conventional transition state theory (TST),[61] which assumes a unity transmission coefficient in the calculated rate constants, the KIE of the Me$_2$NH reaction is defined as the quasi-equilibrium constant in eq 7. Normal and inverse KIEs at a given T would refer to cases in which $K_{q\text{-}eq}$ is greater than or smaller than unity, respectively.

$$\text{Me}_2\text{NH} + \text{AllylCl} \xrightarrow{k_H} \text{TS-H} \quad k_H^{\text{TST}} = \frac{k_B T}{h} e^{-\Delta G_H^{\ddagger}/k_B T} \quad (5)$$

$$\text{Me}_2\text{ND} + \text{AllylCl} \xrightarrow{k_D} \text{TS-D} \quad k_D^{\text{TST}} = \frac{k_B T}{h} e^{-\Delta G_D^{\ddagger}/k_B T} \quad (6)$$

$$\text{Me}_2\text{NH} + \text{TS-D} \xrightarrow{k_{q\text{-}eq}} \text{Me}_2\text{ND} + \text{TS-H} \quad KIE = \frac{k_H^{\text{TST}}}{k_D^{\text{TST}}} = K_{q\text{-}eq} \quad (7)$$

Using statistical mechanics, eq 7 can be evaluated using the partition function ratios as shown in eq 8 where R and TS are the protio reactants and TS of interest, and R* and TS* are the deuterated analogs.

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$$KIE = \frac{k_H^{TST}}{k_D^{TST}} =$$

$$K_{q\text{-eq}} = \left(\frac{Q_{tr}^{R*}Q_{tr}^{TS}}{Q_{tr}^{R}Q_{tr}^{TS*}}\right)\left(\frac{Q_{rot}^{R*}Q_{rot}^{TS}}{Q_{ror}^{R}Q_{rot}^{TS*}}\right)\left(\frac{Q_{vib}^{R*}Q_{vib}^{TS}}{Q_{vib}^{R}Q_{vib}^{TS*}}\right)e^{-\left(\frac{\Delta\Delta ZPE}{RT}\right)} \quad (8)$$

$$KIE = (\eta_{tr})(\eta_{rot})\text{EXC·EXP}$$

where $Q_{tr} = (2\pi M k_B T)^{3/2}/h^3$; $Q_{rot} = 8\pi^2(8\pi^3 I_A I_B I_C)^{1/2}(k_B T)^{1/2}/\sigma h^3$; $Q_{vib} = \Pi_i(1 - e^{-(h\nu_i/k_B T)})^{-1}$ (index "i" scans only real vibrations). $\Delta\Delta ZPE = \Delta ZPE_{TS}^{TS*} - \Delta ZPE_R^{R*}$; $\Delta ZPE_{TS}^{TS*} = ZPE_{TS} - ZPE_{TS*}$; and $\Delta ZPE_R^{R*} = ZPE_R - ZPE_{R*}$. M is the molecular mass, h is Planck's constant, k_B is the Boltzmann constant, T is the absolute temperature, I is the moment of inertia, σ is the symmetry number, and ν_i is the vibrational frequency with the index i covering the modes with real frequencies.

For the S_N2' reaction of $Me_2NH(D)$, η_{tr} and η_{rot} are 1.02 and 1.08, respectively. Together these terms make a normal mass-moment of inertia (MMI) contribution to the calculated KIE. The EXC and ZPE terms on the other hand make inverse contributions, 0.98 and 0.78, respectively. The net isotope effect is 0.84. This means that the deuteriated amine should undergo a slightly faster reaction than the protio amine, in essential agreement with experiment.

To understand why the isotope effect is so small we examine the imaginary frequency, the reaction normal mode of vibration whose zero point energy is lost at the TS, using arguments similar to those we adopted in the analyses of the S_N2 reactions.[60] For most proton transfer reactions this vibration is essentially a movement of the proton from one atom to another. The resulting loss of zero point energy then gives rise to a large primary isotope effect when the proton is replaced by deuterium. The displacement vectors for the S_N2' TS shown in Figure 6 give an entirely different pattern. The dimethylamino group moves as a unit with the nitrogen and its attached hydrogen moving in parallel. This point is emphasized by a comparison of N−H bond distances in dimethylamine, 0.999 Å, TS, 1.007 Å, and reaction product allyldimethylammonium chloride, 1.050 Å. The small change in this bond implies a small isotope effect. Consistent with the absence of any significant loss of vibrational frequency due to breaking the N−H(D) bond in the TS, the calculated imaginary frequencies for the proteo and deuteron TSs are essentially the same (-454 and -452 cm^{-1}). In short, the reaction has little proton transfer character, and the isotope effect is more secondary than primary.

Figure 6 also shows the TS of the S_N2' reaction of allyl chloride with LiCl and the displacement vectors of its imaginary frequency. These show one chloride moving closer to an allyl carbon and the other moving away with lithium moving toward the leaving chloride. This TS is thus different in some fundamental respects from that of the amine reaction.

Conclusions

The computations presented here support our thesis that many of the S_N2' products reported experimentally are probably actually the products of ion pair nucleophiles. The present study shows that ion pair nucleophiles react with allylic halides to form cyclic transition structures stabilized by the attractive electrostatic forces that are more favorable than competing ion pair S_N2 reactions. In particular, the reactive carbon atoms involved in S_N2' reactions remain in their normal tetracoordination compared to S_N2 transition structures in which the reactive carbon is pentacoordinate. The S_N2' transition structures have much of the character of allyl cation−metal dihalide anion ion pairs. Accordingly, substitution of electron donating methyl substituents at the terminal carbon atoms of the allyl halide reduces the energy barrier and facilitates reaction. Cyclic coordination is not as effective in the related reaction of allylic halides with secondary amines and accounts for the low hydrogen isotope effect reported for the amine reaction.

The final conclusion is a recommendation to synthetic chemists. To accomplish S_N2' reactions in competition with S_N2 reactions, it is important to use nonpolar solvents in order to disfavor the free ions that are reactive nucleophiles. Ethers, and particularly THF, are recommended because ionic dissociation is low in such solvents and reactions of ion pairs are more favored. One caveat is that this work has treated only contact ion pair alkali salts; loose or solvent-separated ion pairs would not be expected to conform and most probably would react more like free ions.

Supporting Information Available: Tables of computation results. This material is available free of charge via the Internet at http://pubs.acs.org.

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